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EXAMINER	
ASHEN, JON BENJAMIN	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,724	KINZLER ET AL.	
	Examiner	Art Unit	
	Jon B. Ashen	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-29 and 56-61* is/are pending in the application.

4a) Of the above claim(s) *29,57,59 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,56, 58 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/01/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of group I, claims 27-28, 56, 58 and 60, in the reply filed on 12/21/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of the Application

Claims 27-29 and 56-61 are pending in this application. Claims 29, 57, 59 and 61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/21/2004. Claims 27-28, 56, 58 and 60 are currently under examination in this application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32

USPQ2d 1077 (Fed. Cir. 1994). In the instant case, no disclosure of methods of inhibiting transcription or translation of human MDM2 gene comprising administering an antisense oligonucleotide complementary to contiguous nucleotides selected from nucleotides 1-312 as shown in instant SEQ ID NO: 2 could be located in the claimed priority documents. Therefore, the benefit of priority of claims 27, 28 and 56 is considered to be the filing date of Application 07/867,840, filed 04/07/1992 and the benefit of priority of claims 58 and 60 is considered to be the filing date of the instant application. If Applicant believes that the priority documents provide a disclosure of the specific limitations referred to above, in the context of the claimed invention, they are hereby invited to specifically point to such with particularity.

Claim Rejections - 35 USC § 112

2. Claims 27, 28, 56, 58 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The invention a set forth in claims 27, 28, 56, 58 and 60 is drawn to a method of treating a neoplastic cell comprising administering antisense oligonucleotides which are complementary to human MDM2 mRNA which inhibit transcription or translation of a

human MDM2 gene (claims 27, 28) wherein the oligonucleotides are complementary to contiguous nucleotides selected from nucleotides 1-312 as shown in SEQ ID NO: 2 (claim 58) and to a method of treating a cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein comprising administering antisense oligonucleotides complementary to human MDM2 mRNA which inhibit transcription or translation (claim 56) wherein the oligonucleotides are complementary to contiguous nucleotides selected from nucleotides 1-312 as shown in SEQ ID NO: 2 (claim 60).

Claims 27, 28 and 56 read broadly on a vast number of antisense oligonucleotides that can be any antisense oligonucleotides that are complementary to human MDM2 and that inhibit the transcription or translation of human MDM2 in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein. Claims 58 and 60 read broadly on a vast number of antisense oligonucleotides that can be any antisense oligonucleotides that are complementary to any contiguous nucleotides selected from nucleotides 1-312 as shown in SEQ ID NO: 2 which would include oligonucleotides that are complementary to as few as 2 contiguous nucleotides. All of the aforementioned claims read very broadly on a tremendous number of antisense nucleotide sequences wherein the antisense nucleotide sequence will be sufficiently complementary to any portion of any human MDM2 mRNA (including at least pre-mRNAs, mature mRNAs and transcript variants) or to any contiguous nucleotides from

nucleotides 1-312 as shown in SEQ ID NO: 2, so as to function as an antisense oligonucleotide.

One of skill in the art, however, could not envision, at the time the instant inventions were made, the particular structure of an antisense oligonucleotide that could have been any antisense oligonucleotide that corresponded with the function of inhibiting the transcription or translation of human MDM2 in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein. Additionally, one of skill in the art could not envision the structure of an antisense oligonucleotide that could have been any antisense oligonucleotide of any degree of complementarity to any number of contiguous nucleotides selected from nucleotides 1-312 as shown in SEQ ID NO: 2, including as few as 2 contiguous nucleotides, that would have corresponded with the function of being an antisense oligonucleotide that inhibits the transcription or translation of human MDM2 in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein.

The disclosure of the specification is extremely limited in regards to the methods of antisense inhibition as claimed and merely states, "A further object of the invention is to provide a method of treating a neoplastic human cell" (pg. 5) and "According to another embodiment of the invention, interference with the expression of MDM2 provides a therapeutic modality. The method can be applied *in vivo*, *in vitro*, or *ex vivo*. For example, expression may be down-regulated by administering triple-strand forming

or antisense oligonucleotides which bind to the hMDM2 gene or mRNA, respectively, and prevent transcription or translation. The oligonucleotides may interact with unprocessed pre-mRNA or processed mRNA" (pg. 10, 3rd paragraph).

The specification discloses no examples of antisense oligonucleotides, thereby failing to set forth any representative species of antisense oligonucleotides from within the broad genus of antisense oligonucleotides as claimed. Moreover, neither the specification nor a search of the prior art at the time the invention was made, provides or points to a specific structure of an antisense oligonucleotide, as claimed, that would correspond with the function as claimed. The specification does not disclose any distinguishing identifying characteristics of the genera of antisense oligonucleotides which can be of any degree of complementarity to any human MDM2 mRNA or which can be of any degree of complementarity to any contiguous nucleotides selected from nucleotides 1-312 as shown in SEQ ID NO: 2, that would function in the method as claimed, that would indicate that applicant was in possession of these broadly claimed genera. The specification, therefore, does not provide an adequate written description of the genera of antisense oligonucleotides as claimed, which would indicate that applicant was in possession of said genus. Additionally, the disclosure of the specification provides no specific guidance as to how one skilled in the art might be reasonably led to a particular species of the invention that would function commensurate with the scope what is now claimed, such that the invention would be complete and ready for patenting.

Vas-Cath Inc. v. Mahurkar, 19USPQ2nd 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed (see page 1117). Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). In the instant case, the genera claimed in the instant application are broadly drawn and the

disclosure of the specification is insufficient to show that Applicant was in possession of the claimed invention.

A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

Therefore, Applicant has not provided adequate written description of their invention because Applicant has not shown how they were in possession of the broadly claimed genera of antisense oligonucleotides that would correspond with the function of inhibiting the transcription or translation of human MDM2 in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein. What, in particular, is the structure of an antisense oligonucleotide that can be any antisense oligonucleotide of any degree of complementarity to any human MDM2 mRNA that would correspond with the function of inhibiting the transcription or translation of any human MDM2 gene in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein or the structure of an antisense oligonucleotide that can be any antisense oligonucleotide of any degree of complementary to any contiguous nucleotides selected from nucleotides 1-312 as

shown in SEQ ID NO: 2 that would correspond with the function of being an antisense oligonucleotide that that inhibits the inhibiting the transcription or translation of human MDM2 in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein?

3. Claims 27, 28, 56, 58 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention as set forth in claims 27, 28, 56, 58 and 60 is outlined in a previous rejection herein. In the instant case, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use a method of treating a neoplastic cell or a cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein comprising administering antisense oligonucleotides which are complementary to human MDM2 mRNA or to contiguous nucleotides selected from nucleotides 1-312 as shown in SEQ ID NO: 2, which inhibit transcription or translation of a human MDM2 gene.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the

state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The scope of claims 27, 28, 56, is broadly drawn to methods of *in vivo*, *in vitro* and *ex vivo* treatment comprising administering any number of antisense oligonucleotides that can be any antisense oligonucleotides that are complementary to any human MDM2 (including alleles and transcript variants) and that inhibit the transcription or translation of human MDM2 in neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein. The scope of claims 58 and 60 is broadly drawn to *in vitro*, *ex vivo* and *in vivo* methods of treatment comprising administering any of a vast number of antisense oligonucleotides that can be any antisense oligonucleotides that are complementary to any contiguous nucleotides selected from nucleotides 1-312 as shown in SEQ ID NO: 2, which would include oligonucleotides that are complementary to any 2 contiguous nucleotides.

The specification as filed, however, provides no support for claims to methods of treatment comprising administering antisense oligonucleotides of the invention that inhibit the transcription or translation of human MDM2 mRNA. The specification as filed provides no examples of treatment comprising administering antisense oligonucleotides of the invention and no guidance as to how to make or use the antisense oligonucleotides of the invention that will function to provide a treatment as claimed.

The specification merely asserts that, "A further object of the invention is to provide a method of treating a neoplastic human cell" (pg. 5) and "According to another embodiment of the invention, interference with the expression of MDM2 provides a therapeutic modality. The method can be applied *in vivo*, *in vitro*, or *ex vivo*. For example, expression may be down-regulated by administering triple-strand forming or antisense oligonucleotides which bind to the hMDM2 gene or mRNA, respectively, and prevent transcription or translation. The oligonucleotides may interact with unprocessed pre-mRNA or processed mRNA" (pg. 10, 3rd paragraph). Moreover, the specification as filed provides no specific guidance that would allow the skilled artisan to recognize antisense oligonucleotides that will function in the methods of treatment as claimed.

The state of the art at the time the instant invention was made relative to the enablement of the antisense therapies *in vivo, in vitro* and *ex vivo* recognized that there is a high degree of unpredictability in the art of applying antisense without direct evidence of a therapeutic effect due to numerous obstacles that continue, to the present day, to hinder the application of nucleic acid therapies *in vivo* (whole organism). Such obstacles include, for example, problems with delivery (including uptake by cells) and target accessibility (see below: Agrawal et al., Rojanaskul, Opalinska et al., Jen et al. and Check). At the time the instant invention set forth in claims 27, 28 and 56 was made and even 6 years later, at the time the invention set forth in claims 56 and 58 was made, such obstacles were still relevant to the enablement of antisense inhibition of gene expression *in vitro* (see below: Agrawal et al., Rojanaskul, Opalinska et al., Jen et al. and Check). In particular regard to methods of *in vivo* treatment, cell culture

examples are generally not predictive of *in vivo* inhibition due to differences in metabolites and clearance rates, local concentration of antisense, and the potential for non-antisense side effects. The field of antisense generally, to date, does not provide guidelines by which antisense can be routinely targeted to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a treatment effect. The following references discuss the problems of nucleic acid based therapies in reference to the claimed therapeutic antisense method.

At the time the instant invention set forth in claims 27, 28 and 56 was made, the state of the art, as reviewed by Rojanaskul 1996 (Ad. Drug Deliv. Review. Vol. 18, pp. 115-131, summarized in Abstract), several years post filing, recognized that although oligonucleotide (ON) based therapy had advantages over traditional drugs, "their effective use has been limited due to several problems. For example, naturally occurring ONs contain phosphodiester backbones that are easily degraded in a biological environment and therefore must be protected or modified to render stability. In addition, because of their large molecular size and charge, these compounds are poorly taken up by cells and therefore may not reach their target site. Moreover, problems associated with cellular targeting, potential toxicity and affinity of ONs to the target sites pose major challenges to the successful utilization of these compounds" (Abstract, lines 8-13). Even six years after the invention set forth in claims 27, 28 and 56 was made (the time the invention set forth in claims 56 and 58 was made), Agrawal et al. 2000 (Molecular Medicine Today, Vol. 61, pp. 72-81) indicate, in particular regard to antisense methods of treatment of cells *in vitro*, that, "*In vitro*, cellular uptake of

antisense oligonucleotides depends on many factors including cell type, kinetics of uptake, tissue culture conditions and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide. It is therefore appropriate to study each antisense oligonucleotide in its own context and relevant cell line without generalizing the results for every oligonucleotide" (pg. 80, col. 1, 1st paragraph). It is noted here that the same issues that have been outlined above in regards to *in vitro* enablement of antisense methods of treatment apply to the more complicated endeavor of applying antisense methods of treatment *ex vivo*.

In particular regard to antisense methods of treatment of cells *in vivo*, Opalinska et al. 2002 (Nature Reviews, Vol. 1, pp. 503-514) provide a review of the challenges that remain before nucleic acid therapy becomes routine in therapeutic settings and clearly indicate that the art of nucleic acid therapy remains highly unpredictable and unreliable, particularly *in vivo*. According to Opalinska et al., "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain. The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field" (pg 503). Opalinska et al. also note that .. "[I]t is widely appreciated that the ability of nucleic acid molecules to modify gene expression *in vivo* is quite variable and therefore wanting in terms of reliability. Several

issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" (pg. 511).

In regards to the delivery of therapeutic nucleic acids, Jen et al. (Stem Cells 2000, Vol. 18, p 307-319) state (pg. 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (pg. 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Check also states, in regards to delivery, that ""Scientists tried a variety of ways to get the antisense RNAs into cells ..... [B]ut antisense has not performed well in clinical trials, partly because these delivery systems were not particularly effective. Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. "But we've looked at a lot of the delivery methods that have been used for antisense and so far I haven't been impressed," she says" (pg 11, col. 3, lines 4-15).

The specification as filed provides no guidance that, at the time the invention was made, would have enabled the skilled artisan to have practiced the claimed antisense treatment methods over the broad scope claimed. One of the major obstacles, as shown above, to *in vitro*, *ex vivo* and *in vivo* applications of antisense therapy is the delivery of an antisense molecule to a target cell at a concentration effective to provide

a therapy. The specification does not provide any examples of antisense treatments in neoplastic cells or in cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein or provide any details related to the method of treatment as claimed that would overcome the obstacles outlined above including methods of delivery of antisense to provide a therapy, the local concentration of antisense required to provide a therapy and the potential for non-antisense side effects, for example. Therefore, the specification does not provide, at the time the invention was made, the necessary and specific guidance by which one skilled in the art would have been enabled to deliver antisense targeted to a human MDM2 gene or to nucleotides 1-312 as shown in SEQ ID NO: 2, either *in vitro*, *ex vivo* or *in vivo*, to deliver the antisense of the claimed invention at a concentration effective to provide a therapy.

In order to practice the invention over the full scope claimed, at the time the invention was made, the skilled artisan would have needed to perform undue *de novo* trial and error experimentation, beyond the disclosure of the instant specification, in order to determine how to specifically deliver the claimed antisense *in vitro*, *ex vivo* or *in vivo* to any neoplastic cell or any cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein, at a concentration effective to achieve a therapy. This undue *de novo* trial and error experimentation would have included the determination of such factors as dosage, route of administration, kinetics of uptake, disposition of the antisense molecule in cells, tissues or the human to be treated, and the half-life and stability of the antisense

molecule *in vitro, ex vivo* and *in vivo.* Given the art recognized unpredictability of the application of antisense *in vitro*, *ex vivo* and *in vivo*, at the time the invention was made, this determination would not have been routine. No guidance is provided by the specification for methods of treatment of cells, tissues or a human using MDM2 antisense delivered by any means that would have overcome the obstacles that were recognized in the field of antisense at the time of filing. To overcome those obstacles one skilled in the art would have required specific guidance to predictably apply antisense in methods of treatment as claimed. The specification does not provide this specific guidance for treatment nor did the antisense field at the time of filing have such general guidelines. This is true even to date in regards to *in vivo* therapies. Therefore, to practice the invention in the full scope of what is now claimed, the skilled artisan would have had to perform an extremely large and undue quantity of *de novo* trial and error experimentation (as indicated above).

Therefore, based on the nature of the invention as a method of *in vitro*, *ex vivo* or *in vivo* treatment, the degree of unpredictability in the art of antisense oligonucleotide therapy at the time the invention was made, the breadth of the claimed methods as a method of treatment for any neoplastic cell or any cell having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein, the lack of guidance as to what particular species of antisense oligonucleotides would be required to practice the method as claimed, the need to screen multiple species of said oligonucleotides so as to allow identification of particular species as functional within the method of treatment as claimed and the quantity of *de*

novo experimentation necessary to discover the above, an undue amount of experimentation would be required in order to practice the method of treatment as claimed. Therefore, the inventors have not enabled one skilled in the art to make and use the method of the claimed invention.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 58 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Miraglia et al. (U.S. Patent 6,184,212). The invention as set forth in claims 58 and 60 is outlined in a previous rejection herein. Miraglia et al. disclose and claim a method of reducing hyperproliferation of human cells *in vitro* by inhibiting the expression of human MDM2 using antisense oligonucleotides targeted to nucleobases 1-308 of the 5' untranslated region of human MDM2 (claims 1, 2 and 4). Miraglia et al. disclose SEQ ID NOs: 33-54 which are targeted to nucleotides 4-308 of instant SEQ ID NO: 2. Miraglia et al. further disclose and claim a method of modulating the expression of human MDM2 in cells or tissues comprising contacting said cells or tissues *in vitro* with

the antisense compound of SEQ ID NO: 56 (which targets nucleotide positions 294 to 313 of instant SEQ ID NO: 2) and SEQ ID NO: 57 which targets nucleotide positions 296 to 315 of instant SEQ ID NO: 2). The methods disclosed by Miraglia et al. are methods of treating neoplastic cells or cells having an amplified human MDM2 gene, elevated expression of human MDM2 mRNA or elevated expression of human MDM2 protein in that these methods are broadly drawn to treating any human cells or tissues in vitro using antisense oligonucleotides that are complementary to contiguous nucleotides selected from nucleotides 1-312 of instant SEQ ID NO: 2.

Therefore, each and every aspect of the invention as set forth in claims 58 and 60 is anticipated by Miraglia et al.

Conclusion

6. No claim currently under examination in this application is in condition for allowance or free of the prior art searched.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jba

SEAN McGARRY
PRIMARY EXAMINER
1635